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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,551	09/27/2001	Muthiah Manoharan	ISIS-4847	3873

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EXAMINER

SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
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1635

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8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/965,551	Applicant(s) MANOHARAN, MUTHIAH	
	Examiner James D. Schultz	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 28-30 and 34-51 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 28-30 and 34-51 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____. | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-30, 35-38, 40-43, and 45-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The invention of the above listed claims is drawn to nucleoside compounds containing group R1 which can consist of "a group that enhances the pharmacodynamic

properties of oligonucleotides or a group that enhances the pharmacokinetic properties of oligonucleotides.”

The specification as filed does not contain a description of any representative species that may form the basis for a generic claim to the genus of compounds that may enhance such properties of oligonucleotides, or provide any indication that such a moiety has been reduced to practice or drawings in the instant application. Additionally, no disclosure of relevant identifying characteristics, or description of structures or functions of compounds possessing such enhancing capabilities has been described that might lead one of skill in the art to recognize that applicants were in possession of the claimed genus at the time of filing. Since applicant have not described such characteristics as described above, the skilled artisan would not have been able to envision such compounds that possess the pharmacokinetic and pharmacodynamic properties as claimed.

Claims 28-30 and 34-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of the above claims is drawn to a method of treating organisms having a disease characterized by the undesired production of a protein, comprising contacting said organism with a compound of the above claims. The specification teaches the use of antisense oligos to inhibit the translation of ICAM-1 of cultured cells *in vitro*.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would acknowledge that predicting the efficacy of an antisense compound in treating diseases *in vivo* based solely on results obtained *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo*, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition *in vivo* is highly unpredictable.

Braasch et al. underscore such obstacles in a recent article by stating that “gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable” (Pg. 4503, para. 1 and 2). The unpredictable efficacy of antisense compounds *in vivo* has typically been attributed to the following problems: poor oligonucleotide access to sites within the mRNA to be targeted, delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins. The following references are cited herein to illustrate the state of the art of antisense treatment.

Regarding the difficulties of predicting whether antisense oligonucleotides can access their target, Braasch et al. explains “that it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2).

Branch adds that “internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules” (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

Uptake of oligonucleotides by cells has been addressed by Agrawal, who states, “[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency” (Page 378). “[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations.” (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; “even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins

and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism” (Pg. 4503, para. 1 and 2). Branch affirms that “non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis” (Page 50), while Tamm et al. states that “Immune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally” (page 493, right column).

Further, Branch reasons that “the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available” (Page 46, second column). Tamm et al. concludes by stating that until “the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach.”

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges in the oligo therapy art that are exemplified in the references above.

Further, one skilled in the art would not accept on its face the example given in the specification of the inhibition of I-CAM-1 expression *in vitro* as being correlative or representative of the successful use of antisense compounds *in vivo* for treatment of any and/or all conditions or diseases suspected of being associated with the undesired

production of any protein. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or diseases suspected of being associated with the production of any undesired protein *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by administered antisense oligonucleotides, and specifically regarding the instant methods claimed.

Said claims are drawn very broadly to methods of treating or preventing any condition or disease suspected of being associated with the undesired expression of any protein in an organism. The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with low toxicity that are successfully delivered, and most importantly, that target sites in appropriate cells and /or tissues harboring the undesired protein such that all harmful expression is inhibited, that healthy expression is permitted appropriately *in vivo*, and further, that treatment and/or preventive effects are provided for any and/or all diseases or conditions suspected of being associated with undesired protein production in an organism. Since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being associated with undesired protein production in an organism, and since determination of these factors for a particular target gene in an organism is highly unpredictable, one of ordinary skill in the art would be unable to practice the invention as presented in the specification over the scope claimed.

Furthermore, the instant specification fails to provide one of skill in the art guidance for the selection of successful oligo compounds without undue trial and error experimentation. This is particularly so given that the references above indicate that *in vitro* and cellular screening do not correlate with pharmaceutical oligo compounds that function in an *in vivo* environment. The specification in general fails to provide adequate guidance to overcome the obstacles and unpredictability of oligo therapy that are exemplified in the references above.

Double Patenting

The following rejection is based on U.S. Patent No. 6,326,358, which contains the following (apparent) printer's error; the structure illustrated in claim 1 of said patent exhibits three phosphorus atoms, each bound to one "X₁" moiety. An examination of the patent's specification, and of the corresponding application of said patent reveals that the middle "X₁" of said claim should read as "X₂". The following examination presumes as much.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).


Claims 28-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8, 16 and 27 respectively, of U.S. Patent No. 6,326,358. The instantly claimed invention is drawn to method of treatment using a modified antisense oligonucleotide and thus would be embraced by the claimed invention of U.S. 6,326,358, which is drawn to a method of inhibiting translation of a polypeptide using the same modified antisense oligo as instantly claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:30-5:00 est, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James D. Schultz, Ph.D.
May 30, 2002



ANDREW WANG
PRIMARY EXAMINER